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The Effect of Caraway Seeds Aqueous Extract on Improving Liver and Kidney Functions in Autism Induced by Valproic Acid in Rats.

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Abstract

Autism spectrum disorder (ASD) is a neurological and developmental disorder that affects how people interact with others, communicate, learn, and behave. The present study was designed to investigate the effect of the caraway seeds aqueous extract on improving liver and kidney functions in rats with autism induced by valproic acid. 35 pregnant female rats, 7 of them were used as control and the other 28 received a single oral dose of 800 mg/kg valproic acid VPA on the 12th day of gestation. Their offspring after weaning were randomly distributed into equal groups (n=7) and treated for 25 days as group 1: (Cont-) offspring of control mothers; (Cont+) VPA injection served as control positive; group 3: VPA+ caraway (400 mg/kg b. wt., p.o.);group 4: VPA+ RIS (1 mg/kg b. wt., p.o.); and group 5: VPA+ caraway + RIS. The rats were sacrificed at the end of the experiment and serum was used for the estimation of serum aspartate transaminase (AST), alanine transaminase (ALT), uric acid, urea, and creatinine in addition to the histopathological study of the liver, brain and kidney. The results showed improvement in weight, brain cells , liver, and kidney function by caraway with risperidone treatment in comparison with other treated groups. Conclusion: Consumption of an aqueousextract of caraway seeds had a protective effect due to its effect on brain cells and liver and kidney functions in rats. Consuming caraway seeds has beneficial effects as a functional food in preventing oxidative damage caused by drugs or chemicals.

Keywords: Caraway, Autism, Risperidone drug, Valproic acid.

Introduction

Medicinal plants have become a worldwide topic, having an impact on world health. Herbal medicine has played a crucial role in the maintenance of the healthcare system for a wide population throughout the world **(Meguid *et al.*, 2017).** This is particularly enhanced in less-developed or developing countries, where the history of traditional medicine has been interrupted. The knowledge and progress of the medical benefits of herbs have grown in both, developing and developed countries **(Wei *et al.*,2014).** Medicinal herbs have constituted the basis of alternative medicine and have been the main pathway for conceptualizing new drugs **(Newman *et al.*, 2000).**

Autism spectrum disorder (ASD) is a lifetime neurological illness characterized by social impairments. as well as social and repetitive behaviors. The gender ratio is four males to one female. The cause of autism spectrum disorder cause is unknown, however environmental, and dietary factors influence the disorder **(Bjørklund *et al.*, 2019)**.

Valproic acid (VPA) is an anticonvulsant medication that is mostly used to treat epilepsy, resistant depression, and migraine prevention. Valproic acid was used to produce an animal model of autism spectrum disorder which is the best model for autism because of defective neuronal development in the cerebellum and other brain parts with disruption in synaptic connections. Furthermore, rats prenatally exposed to valproic acid exhibited behavioral characteristics comparable to those of human beings. It certainly constitutes a robust autism model, displaying face, concept, and predictive validity. The valproic acid animal model is a tool for investigating the neurological alterations underlying autism behavior and searching for new therapeutics **(Arafat & Shabaan, 2019).** Valproic acid treatment might cause both reversible and permanent liver damage. Several mechanisms have been postulated to explain valproic acid induced hepatotoxicity, including the formation of reactive valproic acid metabolites, suppression of fatty acid oxidation, oxidative stress, disruption of lipid metabolism, and genetic variants **(Guo *et al.*, 2019).**

Caraway, also known as meridian fennel and Persian cumin (*Carum carvi*), is a biennial plant in the family Apiaceae, native to western Asia, Europe, and North Africa **(Lizarazo *et al.*,2021).** Carum genus has 25 species, of which Carum carvi or caraway is the only annual and biennial economical one as a, a spice, aperitif, and carminative in the foodand pharmaceutical industries. **(Malhotra,2006)**

Caraway is widely used in food products due to its pleasant flavour and preservative properties. Caraway fruits are used as remedies to cure indigestion, pneumonia, and as carminative, appetizer, and galactagogue in different traditional systems **(Rasooli,2016).** According to the European Union herbal monograph, caraway is traditionally used for symptomatic relief of digestive disorders (bloating and flatulence). Caraway fruits possess stimulant, expectorant and antispasmodic effects and is used for stomach aches, constipation, and nausea. It increases the secretion of gastric juice and promotes the discharge of bile, which increases the appetite and has digestive stimulatory effects **(Peter,2006) .** Ibn Sina traditionally used caraway for weight loss **(Nasser *et al.* , 2009),** stomach aches, burping, flatulence and intestinal spasms **(Johri,2011) .** Caraway fruits are the main part of Safoof-e-Mohazzil, which is traditionally used as a weight loss compound **(Agrahari and Singht , 2014) .** In Iranian folk medicine, caraway seeds are believed to possess antiepileptic effects **(Gorji *et al.*,2001) .** Caraway fruits contain valuable therapeutic greenish-yellow essential oil (3-7%), which is used in many therapeutic formulations from ancient times**. (Németh , 2003)**

Risperidone (RIS) Antipsychotic medicines are routinely administered to children with ASD. The Food and Drug Administration (FDA) has authorized risperidone for the treatment of irritability in children with autism disorder, including aggression toward others, self-injuriousness, temper tantrums, and mood swings. **(Hesapcioglu *et al* .,2020).** Antipsychotic medicines have been demonstrated in tests to minimize behavioral difficulties and increase the contextual adaptation of autistic patients. **(Morgano *et al.*, 2020)** Because

risperidone works on serotonin and dopamine, it can be used to treat negative symptoms of schizophrenia while also decreasing positive symptoms **(Pajonk, 2004)** and mild autistic behavior such as mood swings, self-injury, and hostility toward others, especially at low doses. **(Kirino, 2014).**

Therefore, the aim of this study was to investigate the possible improvement of the aqueous extract of caraway seeds intake with or without Risperdal on liver and kidney functions such as ALT, AST, uric acid, urea, and creatinine. The improvement of neurological and hepatic histopathological changes associated with autism may also be considered.

Materials and Methods

Preparation of Caraway Aqueous Extract

The aqueous extractor of caraway was prepared according to by weighing 50 g of caraway seeds and them with an electric grinder to obtain caraway powder. The powder is then dissolved in 1L of distilled water at 37°C and leaves the blend overnight. Finally the mixture was filtered using What man filter paper 41 to remove the impurities. The filtrate was kept in sealed bottles until use**.(Saeed *et al* .,2020)**

Animals: Thirty five female albino rats weighing 180–200 g . The rats were kept in plastic cages, seven pregnant female rats per cage. Throughout the experiment, animals were maintained at a constant temperature of 25 2 °C and under a 12-hour light/12-hour dark cycle. During the trial, a commercial mouse pelleted food was given. Before the trial started, the animals were given two weeks to get used to the lab environment. Ad libitum access to food and water was provided, and weight gain was monitored biweekly. The state authorities approved the experimental techniques and procedures, and they conformed to ethical guidelines for animal protection .At 25 days old, the rat's offspring were sacrificed, and the tissues were removed and kept at −70 °C until the assays were performed. Serum was extracted for biochemical study, and liver, kidneys and brains were isolated and presented in 10% formalin for the histological study.

Materials:

Drugs Sodium valproate: VPA Sodium Salt 98% was purchased from, Sigma, St. Louis, MO, USA,and Risperidone oral solution was purchased from JANSSEN CILAC.

Experimental design of biological study: The female rats were mated overnight, and vaginal lavage was the way to check for the existence of the sperm. The first day of gestation was chosen to be the day when the smear was sperm positive.

On the 12th day of gestation, the rats were divided into two main subgroups: the first one included 7 animals treated with the vehicle. Rest of the 28 animals were treated with VPA (800 mg/kg, orally) **(Ali & Elgoly, 2013).** On the 25th day of birth, the offspring male was randomly distributed into five groups: The first group 1 (control -): These include 7 male offspring of the mother group who received oral saline. The second group (VPA - Control +): These include 7 male offspring of the mother group who received oral VPA. The third group (VPA+ The aqueous extract of caraway seeds): These include 7 male offspring of the oral VPA mother group who were orally gavage 400 mg/kg/day of the aqueous extract of

caraway seeds **(Biozid *et al.*, 2020).** The fourth group (VPA+Risperdone): These include 7 male offspring of the oral VPA mother group who were orally gavaged with 1gm/kg/day **(Ali *et al.*, 2020)** The fifth group (VPA+ the aqueous extract of caraway seeds + Risperidone): These include 7 male offspring of the oral VPA mother group who received the aqueous extract of caraway seeds and Risperdone at the dosage mentioned in the previous groups.

Biochemical assay:

Chemical composition of caraway: Caraway seeds were obtained, and chemically analyzed at the Institute of Food Technology, Giza, Egypt. Alanine aminotransferase activities (ALT) were measured in serum using the modified kinetic**.** Aspartate amino Transferase (AST) activities were measured in serum using the modified kinetic methods. **(Reitman & Frankel, 1957)** . Uric acid was assessed according to the method described by **Fossati *et al*. (1980**). **(Fawcett & Scott, 1960)** .Creatinine was measured using a modified kinetic method. **(Bartels *et al*., 1972) (Larsen, 1972).**

Histopathology Examinations: Small specimens of the liver, kidney and brain organs were taken from each experimental animal, fixed in neutral buffered formalin 10%, cleared in xylene, and embedded in paraffin. Sections of 4- 6 mm thicknesses were prepared and stained with hematoxylin and eosin.

Statistical analysis: The results were reported as mean ± standard error (SE). SPSS software (version 27) was used to do the statistics analysis (one-way analysis of variance (ANOVA) followed by the LSD test). to determine the statistical significance f the difference according to **Snedecor and Cochran (1989).** The significance level was set at $p \leq 0.05$ and $p \leq 0.01$.

RESULT

The data in Table (1) shows the chemical composition of caraway seeds/100g. It contains 9.71% water, 11.31 grams of protein, 355 calories, 9.4 grams of fat, and 56.3 grams of carbohydrates.

Table (1): Chemical composition of caraway seeds /100g

Nutrients (%)	Amounts
Water (g)	9.71
Protein (g)	11.14
Energy (Kcal)	355
Lipids (g)	9.04
Total carbohydrates (g)	55.91
Fiber (g)	11.03
Ashe (g)	3.7

Calcium (mg)	694
Phosphorus (mg)	622
Magnesium (mg)	237
Potassium (mg)	1280
Zinc (mg)	5.8
Sodium (mg)	18
Vitamin A (IU)	365

The data presented in Fig. (1) show the growth weight chart of different treated groups of offspring rats during the period of the experiment. The data showed a significant decrease in all treated groups as compared to the control group in the first, 15 th, and 25 th days after weaning.

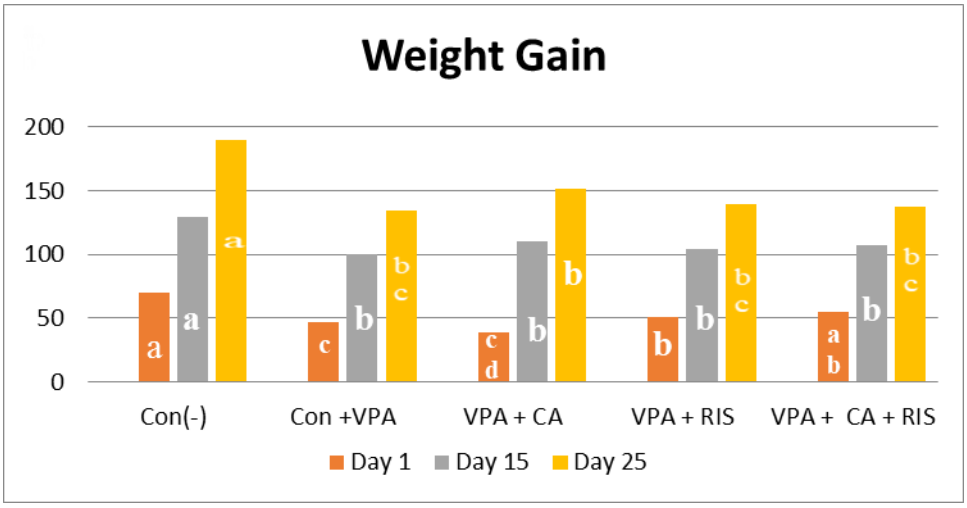

Fig (1) show the growth weight chart of different treated groups

CON= Control, VPA= Valporic acid , CA = caraway and RIS= Risperidone.
* Non significant differences between the values had the same letter.
* LSD: Least Significant Difference at level 0.05

Figure (2): Shows a significant increase in the serum AST and ALT activity in VPA treated rats was noted, compared to the control and VPA+ CA group. While the VPA group did not show significance with VPA+RIS and VPA+CA+RIS. Moreover, the VPA+CA group exhibited no significant decrease when compared to the VPA+RIS and VPA+ CA +RIS and control groups.

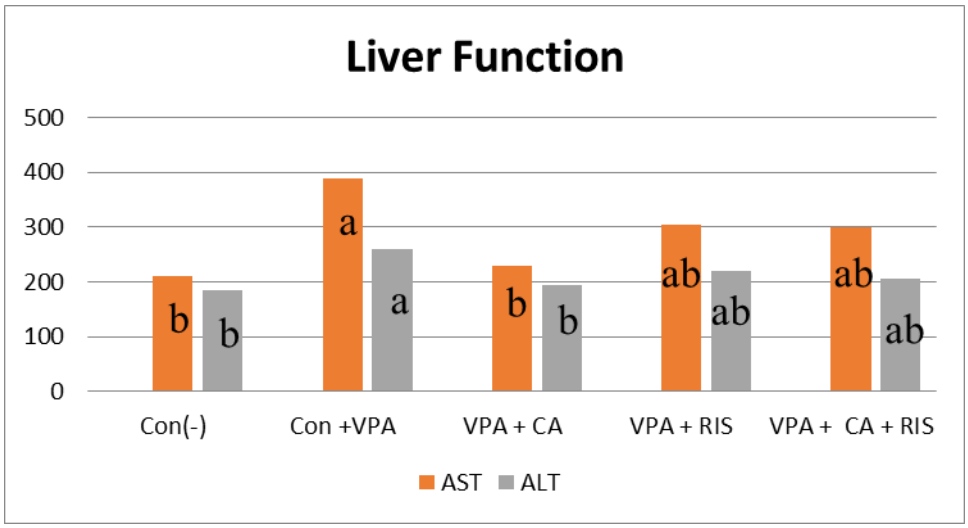

Fig (2): Shows the serum AST and ALT levels

CON= Control, VPA= Valporic acid , CA = caraway and RIS= Risperidone.
* Non significant differences between the values had the same letter.
* LSD: Least Significant Difference at level 0.05

The VPA-treated rats group exhibited a significant increase in serum uric acid and creatinine level when compared to the control (-) and VPA+ CA group (Fig. 3). While VPA+ CA +RIS showed a significant increase in creatinine levels in comparison with VPA+RIS and the control group and not sig. to VPA+ CA groups. On the other side, the VPA+RIS group showed a significant decrease in comparison with the VPA, VPA+ CA, and VPA+ CA + RIS for creatinine level. Also, all treated groups exhibited a significant decrease in uric acid and creatinine levels in comparison with control (+).

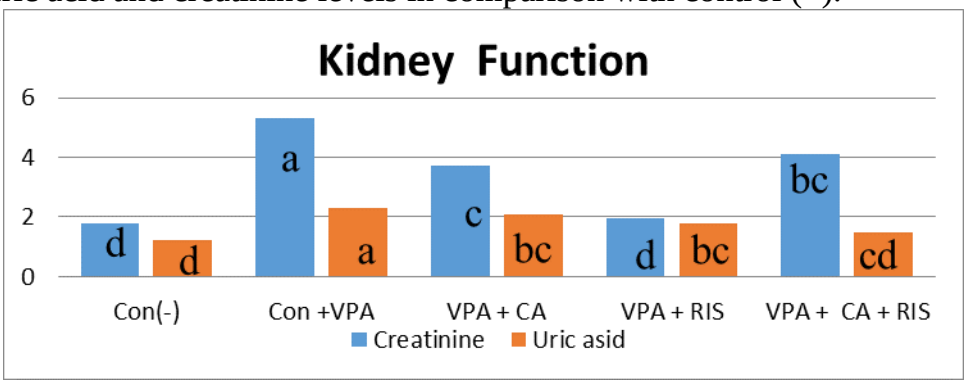

Fig (3): Shows the serum creatinine and uric acid levels

CON= Control, VPA= Valporic acid , CA = caraway and RIS= Risperidone.
* Non significant differences between the values had the same letter.
* LSD: Least Significant Difference at level 0.05

The data cleared in Figure (4) shows the effect of different treatments with VPA (positive control), CA, RIS, and CA + RIS. Also, both CA , RIS and CA+RIS enhance the

urea values add these are in order: VPA+ CA +RIS, VPA+RIS, VPA+ CA compared to VPA positive control.

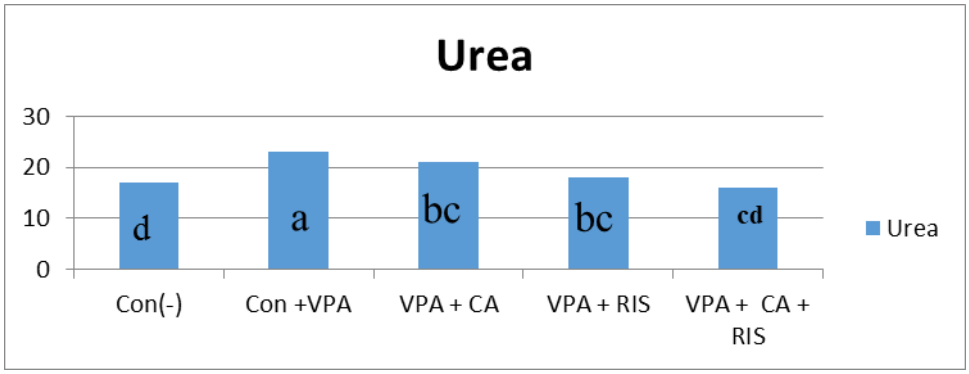

Fig (4): Shows the urea levels

CON= Control, VPA= Valporic acid , GA= caraway and RIS= Risperidone.
* Non significant differences between the values had the same letter.
* LSD: Least Significant Difference at level 0.05

Histopathology Examinations:

Effect of a caraway aqueous extract on liver histopathology:

Effects of caraway extracts on liver histopathology sections of group 1(Control) rats, livers showed normal hepatocytes (Photo 1). Liver sections of VPA group 2rats showed severe vacuolar degeneration of the hepatocytes with inflammatory cell infiltrations around blood vessels (Photo 2). (Photo 3). Liver sections of group 3 (VPA+ CA) rats showed apparently normal structure except for slight vacuolar degeneration of hepatocytes with pericentral inflammatory cell infiltrations (Photo 4). Liver sections of group 4(VAP + RIS) rats showed vacuolar degeneration of hepatocytes with inflammatory cell infiltrations around the blood vessels (Photo 5). The liver sections of group 5 (VAP +CA+ RIS) rats showed normal structure except for the slight degeneration of hepatocytes.

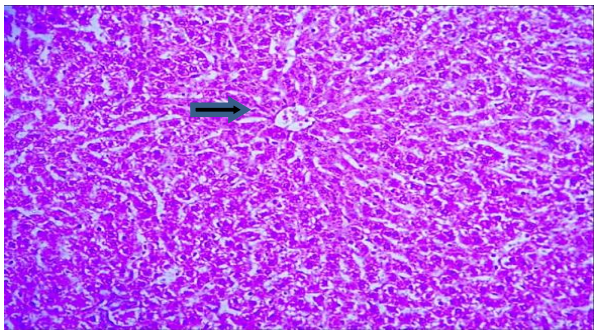

Photo (1): Liver section of a rat from control group showed apparently normal hepatocytes and portal vein (arrow) (H & E x 200).

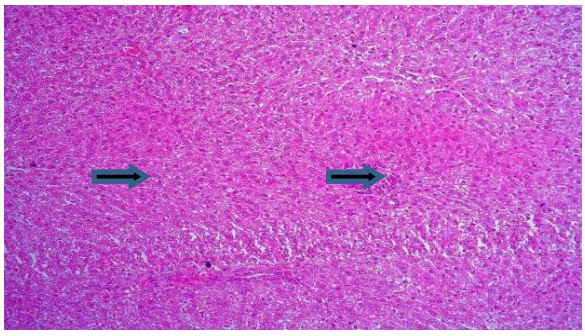

Photo (2): Liver section of a rat from VPA group showed severe vacuolar degeneration of hepatocytes (arrows) with inflammatory cells infiltrations around blood vessel (star) (H & E x 200).

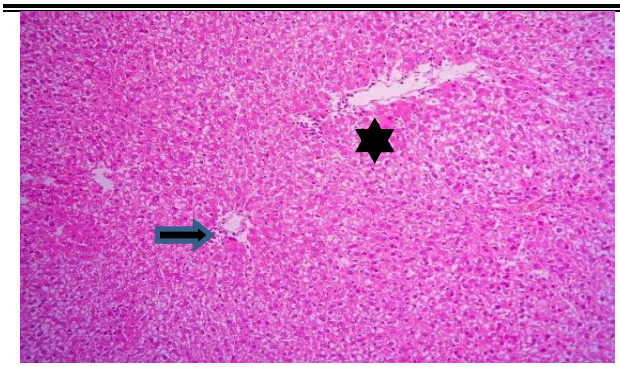

Photo (3): Liver section of a rat from (VPA+ CA) group showed apparently normal structure except slightly vacuolar degeneration of hepatocytes (arrow) with mild pericenteral inflammatory cells infiltrations (star) (H & E x 200)

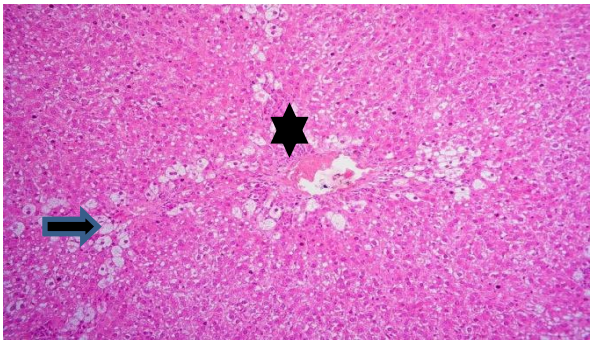

Photo (4): Liver section of a rat from (VAP + RIS) group showed vacuolar degeneration of hepatocytes (arrow) with inflammatory cells infiltrations around blood vessel (star) (H & E x 200).

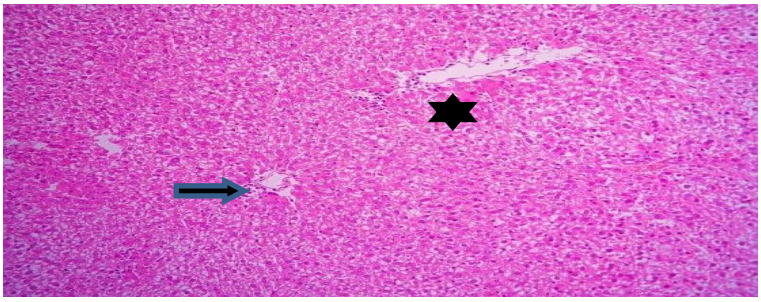

Photo (5): Liver section of a rat from (VAP +CA+ RIS) group showed apparently normal structure except slight degeneration of hepatocytes (arrow) (H & E x 200).

Effects of caraway extracts on cerebral cortex micrograph:

The following figures are showing group 1 normal histological structure which consisted of several layers of neuronal cells arrow group2 Neuronal degeneration, per-vascular and peri-neuronal oedema arrow group3 mild neuronal swelling and neuronophagia arrow group4 Neuronal degeneration with neuronophagia, gliosis and pericellular edema arrow group5 a large number of intact neuronal cells arrow (H&Ex400).

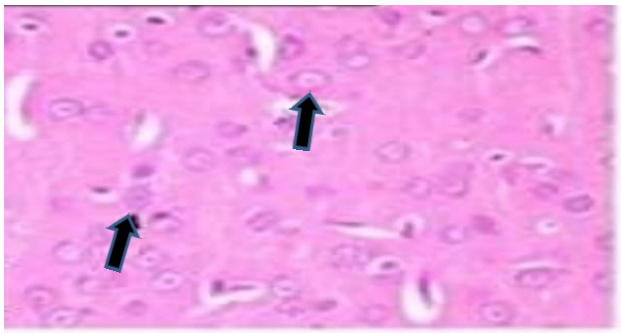

Photo (6): Cerebral cortex brain micrograph in control group showing normal histological structure which consisted of several layers of neuronal cells arrow. (H&Ex400).

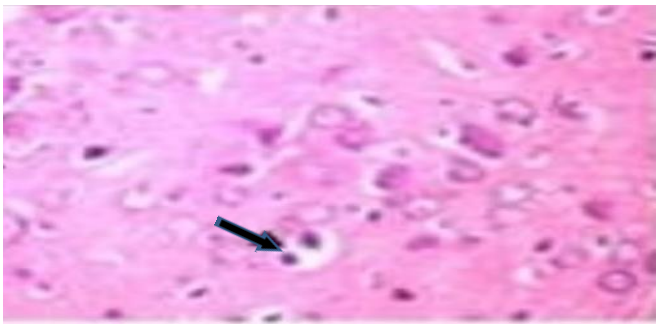

Photo (7): Cerebral cortex brain micrograph in VPA group showing neuronal degeneration, per-vascular and peri-neuronal oedema arrow. (H&Ex400).

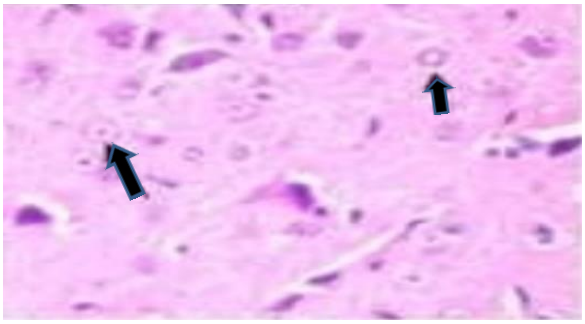

Photo (8): Cerebral cortex brain micrograph in (VPA+ CA) group showing mild neuronal swelling and neuronophagia arrow. (H&Ex400).

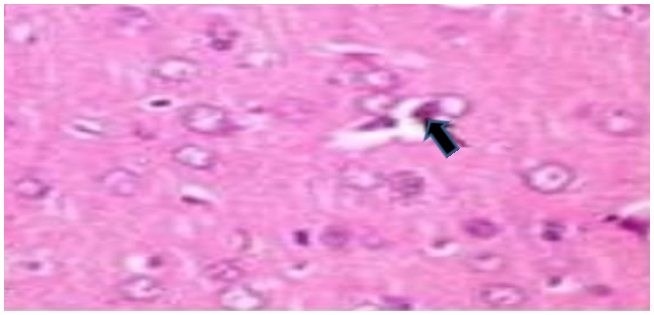

Photo (9): Cerebral cortex brain micrograph in (VPA+ RIS) group showing neuronal degeneration with neuronophagia, gliosis and pericellular edema arrow. (H&Ex400).

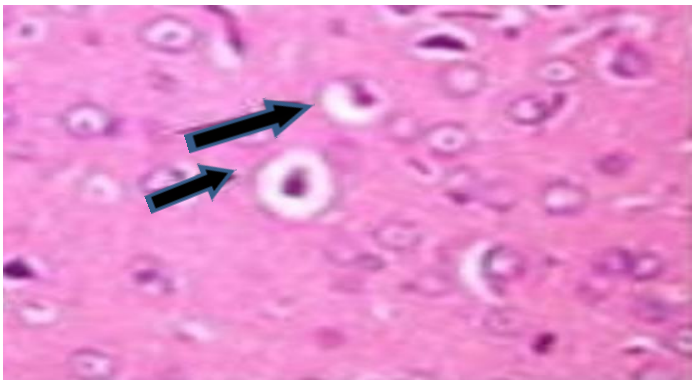

Photo (10): Cerebral cortex brain micrograph in (VPA+ CA+ RIS) group showing a large number of intact neuronal cells arrow (H&Ex400).

Effect of a caraway aqueous extract on kidney histopathology:

Sections of group 1(Control) rats, kidneys showed normal renal tubules and glomerular tufs (Photo 11). Kidney sections of VPA group 2rats showed necrosis and degeneration of epithelial lining renal tubules together with glomerular tufts and inflammatory cell infiltrations (Photo 12). A high power photo showed inflammatory cell infiltrations, interstitial hemorrhages, widening space of Bowman's capsule severe necrosis, and degeneration of epithelial lining renal tubules and glomerular tufts (Photo 13). Kidney sections of group 3 (VPA+ CA) rats showed apparently normal structure except for mild degeneration of the epithelial lining renal tubules with presence of hyaline casts within a few renal tubules (Photo 14). Kidney sections of group 4(VAP + RIS) rats showed vacuolation of the blood vessel wall with perivascular connective tissue proliferation (Photo 15). The kidney sections of group 5 (VAP +CA+ RIS) rats showed apparently normal structure except slightly vacuolation of the blood vessel wall with perivascular connective tissue proliferation, narrow space of Bowman’s capsule.

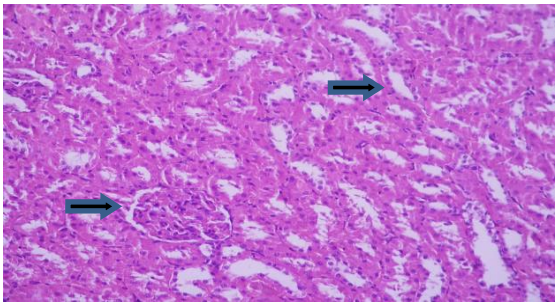

Photo (11): Renal section of a rat from control group showed normal renal tubules, glomerular tuft, and Bowman's capsule (arrow) (H & E x 200).

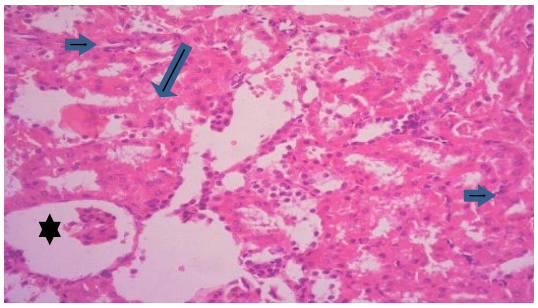

Photo (12) Renal section of a rat from VPA group showed inflammatory cells infiltrations (arrow), interstitial haemorrhages (large arrow), widening space of Bowman's capsule (star) severe necrosis, and degeneration of epithelial linning renal tubules and glomerular tufts(H & E x 400).

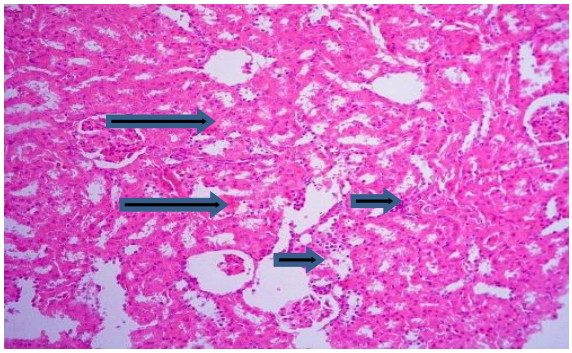

Photo (13): Renal section of a rat from (VPA+ CA) group showed necrosis and degeneration of epithelial lining renal tubules (arrows) together with some glomerular tufts and inflammatory cells infiltrations (large arrow) (H & E x 200).

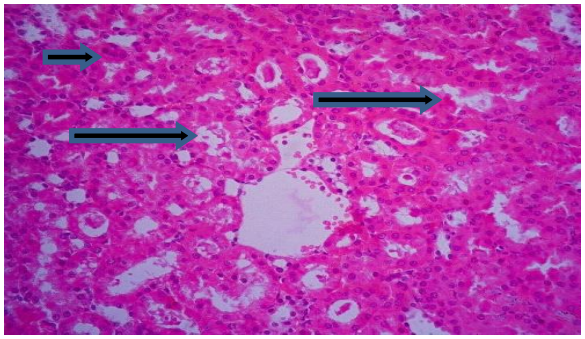

Photo (14): Renal section of a rat from (VPA+ RIS) group showed vacuolation of the blood vessel wall (arrow) with perivascular connective tissue proliferation (large arrow) (H & E x 200).

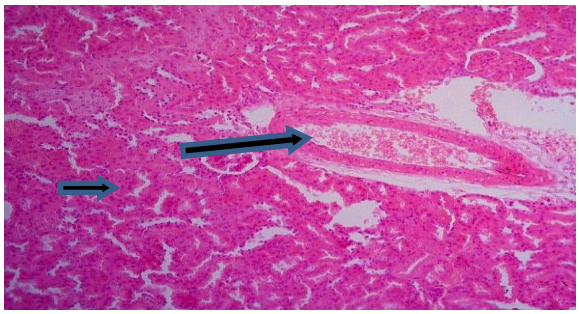

Photo (15): Renal section of a rat from (VPA+ CA+ RIS) group showed apparently normal structure and Bowman's capsule except slightly vacuolation of the blood vessel wall (arrow) with perivascular connective tissue proliferation (large arrow) (H & E x 200).

Discussion

Autism Spectrum Disorder is a neurodevelopmental disorder caused by a lack of verbal and nonverbal communication, social skills, and relationships **(Wei *et al.*, 2014).** The underlying cause of autism spectrum disorder is still unidentified. As a result, the current study was carried out to better understand the relationship between the biochemical and histological aspects of autism.

We concentrated on the way of performing the autism Spectrum Disorder animal models. Despite the significant evidence for genetic links to autism, an early environmental injury is

still an increasing worry, especially given the recent increase in autism prevalence **(Fombonne, 2005).** This model, which represents one of the environmental causes of autism, may more accurately represent idiopathic autism than transgenic mice that have mutations in specific autism-associated genes **(Nicolini & Fahnestock, 2018)**. Due to its ability to cause autism when administered early in pregnancy, we considered valproic acid (VPA) as a useful model of autism **(Stadelmaier *et al.*, 2017).**

Newborns exposed to prenatal valproic acid had delayed maturation as seen by reduced body weight, a minor decrease in brain weight, and delayed eye opening, suggesting potentially altered neurodevelopmental consequences **(Al-Askar *et al.*, 2017).** The rodent model of autism was created by the exposure of rat fetuses to valproic acid on the 12.5th day of gestation (VPA rats). The model and human data show strong anatomical, pathological, and etiological parallels, Furthermore, VPA rats displayed slower maturation and reduced body weight **(Schneider & Przew\locki, 2005).**

Valproic acid was linked to several significant side effects in the blood, pancreatic, hepatic, and renal functions. It has been established that VPA is a teratogen that induces abnormalities in the neural tube. The research mentioned that VPA may harm the liver and induce pancreatitis. Additionally, it has been suggested that one of the frequent adverse effects of VPA therapy is liver impairment. Research has shown that the VPA impact led to liver biopsy findings of cholestasis, significant bile duct loss, and portal inflammation. Uncertainty persists regarding how VPA alters the metabolism of lipids to lead to a fatty liver. Additionally, it has been shown that VPA has a critical function in the degenerative alterations that occur in pregnant rats' kidneys **(Amoudi, 2017).**

Long-term treatment medications, such as RIS, should consider the risk of hepatotoxicity and renal impairment in addition to severe metabolic and inflammatory consequences **(Papatriantafyllou *et al.*, 2022).** According to the study, rats given RIS exhibited hepatotoxicity, including zonal necrosis and partial obstruction of the central vein **(Bariweni *et al.*, 2022).**

Additionally, a severe case of hepatic damage can progress into acute or chronic liver failure, showing signs of cellular swelling and lysed cells that leak intracellular fluid into the environment, finally triggering an inflammatory response **(Guicciardi *et al.*, 2013).**

The mechanism behind risperidone-associated metabolic abnormalities and hepatic and kidney side effects requires additional investigation. Recent data show that risperidone can raise blood ALT and AST levels (a liver inflammation indicator) in mice. Upon that, serum ALT and AST levels were determined. Long-term therapy with risperidoneinducing visceral obesity linked with cholestatic hepatitis and hepatic steatosis resulted in similar findings in mice and people. Furthermore, an analysis of liver enzymes demonstrated that risperidone caused liver damage in rats by increasing free radical damage and decreasing plasma total antioxidant activity. Risperidone's actions finally resulted in hepatic adverse effects due to the stimulation of hepatic lipogenesis **(Tsai *et al.*, 2021).**

According to our research, rats with chemically induced acute liver damage may benefit from the curring benefits of caraway extracts. The prevention of lipid peroxidation by-products as well as increased antioxidant enzymes are most likely what causes caraway extracts to have therapeutic/hepatoprotective benefits **(Sharifudin *et al.*, 2013).**

Caraway seemed to provide defense and preserve the hepatocellular membrane's structural integrity. This was clear from the substantial decrease in AST and ALT levels, which showed that treated rats were protected against antitubercular medication toxicity. Our results agreed with a study that reported that a caraway extract has lower levels of AST and ALT in hepatotoxicity (**Pari & Kumar, 2002**). The study found that blood urea levels in RIS-treated rats significantly increased as compared to serum urea levels in control rats and rats that had received caraway extract as a pretreatment. The amount of urea is used to measure renal function and won't increase until at least half of the kidney's nephrons have been destroyed. The antioxidant qualities of the plant may have prevented oxidative damage to the kidney's microstructure, which may have contributed to the near-normal urea content shown in the rats pretreated with an extract of caraway in this study. Rats exposed to VPA developed liver and renal damage, while an extract of caraway had significant promise for protection **(Ajilore *et al.*, 2012).**

An earlier study discovered that caraway extract enhanced the healing of liver cells. The capacity of caraway and silymarin to cure the hepatic damage was equivalent, there was demonstrated by the histological observation. The study of the liver and kidney tissues was supported by hepatoprotective investigations. The advancement of the hepatocellular damage seen in histological investigations was effectively prevented by the caraway extracts. The effects of the extract treatments significantly decreased the number of necrotic hepatocytes and inflammatory cell infiltration, which prevented further liver damage. These results point to the tissue-protective properties of caraway extracts in rats exposed to toxic chemicals. The hepatoprotective impact of the caraway extract on liver damage has shown a significant protective function because of its influence on the levels of aspartate aminotransferase, alanine-aminotransferase, and lipid peroxidation in the liver (**Sharifudin et al., 2013).**

In contrast, the hepatic tissues taken from the group which received VPA indicated significant alterations in intrahepatic blood vein congestion. Furthermore, quantities of the leukocyte inflammatory cells were seen infiltrating this area of the group which received VPA. It is worth noting that following VPA exposure, most of the hepatocytes had cytoplasmic vacuolation with pyknotic nuclei, congestion, fibrosis, and bile duct necrosis surrounding the portal tract, as well as fatty infiltrations in the VPA group.

Microscopical examination of the kidneys of VPA-treated rats revealed congested and enlarged renal veins, as well as vacuolar degeneration in certain tubular epithelial cells and cell debris, dispersed in tubular lumina. The renal tubules had cytoplasmic vacuolation of the epithelial lining and proteinaceous casts in their lumen. In addition, an edematous lesion was seen between the tubules. The renal tubules seemed seriously damaged, with fractured and degraded glomeruli **(Ali *et al.*, 2020).**

In addition, the groups who had received caraway as a pretreatment showed notable preservation of liver histology. The return of the enzyme levels to normal after caraway treatment revealed that caraway extract may play some functions in maintaining the structural integrity of the hepatocellular tissue and preventing enzyme leakage into the bloodstream**.(Amoudi,2017)**

The commonly held belief that transaminase levels will recover to normal is supported by our findings. This study also revealed that therapy with caraway decreased the levels of elevated blood uric acid, urea and creatinine, which suggests that the caraway's components not only preserved the kidney's structural integrity but also enhanced its ability for regenerative and reparative processes **(Kazemipoor *et al.*, 2014).**

A synergy was observed in the group treated with VPA + CA + RIS compared to the group treated with VPA + CA, which showed an improvement in body weight, serum aspartate aminotransferase activity, and serum creatinine content. This improvement is likely due to the desirable therapeutic compounds found in caraway **(Chhikara *et al.*, 2020).**

Conclusion:

In conclusion, the aqueous extract of caraway stimulated the functions of the liver, kidneys, and brain cells. These results support the idea that there are high levels of bioactive components in caraway extract. These results also highlight the importance of consuming caraway seeds due to their beneficial effects as a functional food in the prevention of oxidative damage caused by drugs or chemicals.

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تأثير المستخلص المائي لبذور الكراوية على تحسين وظائف الكبد والكلى في مرض التوحد المحدث بحمض الفالبرويك في الفئران

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الملخص

اضطراب طيف التوحد (ASD) هو اضطراب عصبي وتنموي يؤثر على كيفية تفاعل الأشخاص مع الآخرين والتواصل والتعلم والتصرف. لقد كان مرض التوحد في ارتفاع بمعدل ينذر بالخطر على مدى العقود الثلاثة الماضية، في حين يبدو أن معدل التكرار يختلف من بلد إلى آخر. صممت هذه الدراسة لمعرفة تأثير المستخلص المائي لبذور الكراوية على وظائف الكبد والكلى والتغيرات التشريحية المرضية في الفئران مقارنة مع عقار الريسبيريدون الكيميائي على الفئران المحدثة بالتوحد بواسطة حمض الفالبرويك. و تم استخدام 35 فأراً حاملاً، 7 منها كمجموعة ضابطة سالبة بينما تلقت 28 أخرى جرعة فموية واحدة قدرها 800 ملغم/كغم من حمض الفالبرويك VPA في اليوم الثاني عشر من الحمل، ثم تم أخذ نسلهن بعد الفطام عشوائياً إلى مجموعات متساوية (ن =7) وعولجت لمدة 25 يومًا كالتالي مجموعة 1: نسل أمهات المجموعة الضابطة السالبة ،مجموعة 2: مجموعة VPA كانت بمثابة (مجموعة ضابطة موجبة) ، المجموعة 3:VPA +الكراوية (400 / ملجم / كجم بالوزن)، المجموعة 4: VPA+ RIS (1ملجم/كجم من وزن الجسم)، والمجموعة 5: VPA + الكراوية +RIS ثم تم ذبح الفئران في نهاية التجربة واستخدام المصل لتقدير أنزيمات الكبد (AST)، (ALT)،ووظائف الكلي: حمض البوليك، اليوريا، والكرياتينين بالإضافة إلى فحص الأنسجة للكبد والدماغ و الكلي. و أظهرت النتائج تحسنا في الوزن وخلايا المخ والكبد ووظائف الكلى عند تناول الكراوية مع دواء الريسبيريدون مقارنة مع المجموعات المعالجة الأخرى. الخلاصة: إن استهلاك المستخلص المائي لبذور الكراوية له تأثير وقائي بسبب تأثيره على خلايا المخ ووظائف الكبد والكلى في الفئران. كما أن استهلاك بذور الكراوية له آثار مفيدة كغذاء وظيفي في منع الأضرار التأكسدية الناجمة عن الأدوية أو المواد الكيميائية.

الكلمات المفتاحية: الكراوية، التوحد، دواء الريسبيريدون، حمض الفالبرويك.